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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/607,974	SERRERO, GINETTE	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/14/03 & 10/8/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Preliminary Amendment filed August 14, 2003.

Claims 1-27 have been canceled. Claims 28-37 are pending in the instant application.

Claims 28-37 have been examined on the merits.

Priority

Applicant's reference to priority in the first sentence of the specification is acknowledged. It is noted that the instant application has been afforded priority to USSN 08/863,079, filed on May 23, 1997.

Information Disclosure Statement

Applicant's information disclosure statement filed August 14, 2003 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Applicant's information disclosure statement filed October 8, 2003 is acknowledged. The submission is not in compliance with the provisions of 37 CFR §1.98 since a column has not been provided that that contains a space, next to each

document to be considered, for the examiner's initials. Additionally, the submission does not identify each U.S. patent application by the inventor, application number, and filing date. Accordingly, the information disclosure statement filed October 8, 2003 has been placed in the file, but it has not been considered by the Examiner. A lined through copy indicating that the applications have not been considered is enclosed herewith.

Specification

It is noted that the instant specification at pages 77-87 lists numerous non-patent literature. If Applicant's wish to have these references considered by the Office, Applicants should include them in an information disclosure statement filed under 37 CFR § 1.97.

The use of the trademarks Trizol and RNAzol have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Appropriate correction is required. It is noted that the Examiner has not made an exhaustive review of the application. Applicants are urged to review the disclosure and use capitalized, generic terminology of trademarks.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-7 and 10 of U.S. Patent No. 6,670,183 ('183). Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter as follows: The method of inhibiting the production or biological activity of GP88 *ex vivo* or *in vitro* comprising the steps of administering an antisense oligonucleotide that inhibits the production or biological activity of GP88 of ('183) is fully encompassed in the methods as instantly claimed since the methods of the patent and the methods as instantly claim recite the

same method step, namely the administration of a GP88 antisense oligonucleotide. Since the methods recited in the patent recite the same method step as those instantly claimed, the methods of the patent would inherently inhibit the growth of a tumor cell, inhibit GP88 protein expression, or inhibit the proliferation of a tumor cell as claimed in the instant application. It is noted that the methods as instantly claimed are given their broadest reasonable interpretation and encompass both *in vitro* or *ex vivo* methods. See MPEP §2111-2116.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-37 are indefinite because the term "GP88" is not clearly defined. Since abbreviations often have more than one meaning, it is suggested that inserting the full name of the growth factor would overcome the instant rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the growth of a tumor cell or a method of inhibiting the protein expression of 88kDa glycoprotein growth factor (GP88) in a cell, comprising the subcutaneous injection of a GP88 antisense targeted to SEQ ID NO:16, using primer pairs SEQ ID NO:12 and SEQ ID NO:14, wherein said antisense inhibits the growth of the tumor cell or inhibits the protein expression of GP88, does not reasonably provide enablement for a method of inhibiting the growth of a tumor cell or a method of inhibiting the protein expression of GP88 in a cell, comprising any route of administration of any antisense targeted to GP88, wherein said antisense inhibits the growth of the tumor cell or inhibits the protein expression of GP88. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

Claims 28-33 are drawn to a method of inhibiting the growth or size of a tumor cell comprising administering a GP88 antisense oligonucleotide wherein said antisense inhibits the growth or decreases the size of the tumor cell. Claim 34 is drawn to a method of inhibiting the protein expression of GP88 in a cell comprising administering a

GP88 antisense oligonucleotide wherein said antisense inhibits the protein expression of GP88. Claims 35-37 are drawn to a method of inhibiting the proliferation of a tumor cell comprising administering a GP88 antisense oligonucleotide wherein said antisense inhibits the proliferation of the tumor cell. Applicant is reminded that that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP §2111-2116.01. The instant specification discloses, "the antisense oligonucleotides of the invention are also used as a treatment for cancer in cells which exhibit an increased expression of GP88" (see the instant specification at page 12 paragraph [0046]). Consistent with the instant specification, the Examiner is broadly interpreting the claims to read on a method for administering a GP88 antisense to cells *in vivo* for the purpose of treating cancer, for example.

The instant specification teaches that a 400-bp antisense cDNA construct of human GP88 inhibits GP88 protein expression and tumor growth in nude mice following subcutaneous injection in the breast area (see Examples 9-11, Table 3, and Figures 3, 4, and 15). It is well known in the art that the activity of a particular antisense depends greatly on its specific sequence. For example, Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6:72-80) teach, "The initial step in selecting an antisense oligonucleotide is to choose an appropriate target sequence on the mRNA molecule. Antisense technology has been hampered to some extent by limited knowledge as to the base-pairing accessibility of mRNA target sites *in vivo*. Although a number of models that predict RNA folding are available, their use-fullness for predicting the most plausible *in vivo*" RNA structure is limited (see page 76, last paragraph). Agrawal et al.

go on to teach, "The affinity of an oligonucleotide for its target RNA varies significantly depending on base composition and sequence. Therefore, the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence" (see page 77, second column, first paragraph). Therefore, the feasibility of antisense therapy for one antisense does not demonstrate the feasibility of antisense therapy for a wholly different antisense oligonucleotide, since the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence, as taught by Agrawal et al.

The feasibility of antisense therapy for one antisense does not demonstrate the feasibility of antisense therapy for a wholly different antisense oligonucleotide is best demonstrated by Zhang et al. (Proc. Natl. Acad. Sci., 1998 Vol. 95:14202-14207) who disclose the *in vivo* tumorigenicity of three antisense cDNA targeted to PCDGF (also known as GP88). Two PCDGF antisense, ASII1 and ASII18, were not tumorigenic since none of the injected mice developed tumors following antisense administration. However, one antisense, ASII15, maintained some degree of tumorigenicity since two of the five mice developed small tumors following antisense administration.

At the time the instant Application was filed, and even to date, antisense based therapies were highly unpredictable. Even with the advances made by the field of antisense technology, antisense oligonucleotides are still recognized in the art as not enabled for therapeutic purposes. See for example, Jen et al. (Stem Cells, 2000 Vol. 18:307-319), Branch, AD (TIBS, 1998 Vol. 23:45-50, Applicants reference CEEE, submitted in the information disclosure statement filed August 14, 2003), and Agrawal et

al. for a review on the progression of antisense therapy *in vivo* (whole animals) and the state of the art of antisense therapy for therapeutic purposes. For example, Jen et al. state, "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery... Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable" (see page 313, second column, second paragraph). Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive" (see page 315, second column). Branch addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise of rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying

mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo.*"

Furthermore, the claims are so broad to include any route of administration of the GP88 antisense oligonucleotide, including systemic administration, where only subcutaneous administration of the GP88 antisense is demonstrated in the instant specification. It is well established in the art that there is a significant level of unpredictability regarding the delivery of oligonucleotide-based therapeutics. For

example, Nielsen, PE (Gene Therapy, 2005 Vol. 12:956-957) reviews the problems associated with nucleic acid-based therapeutics and systemic delivery. Nielsen, PE teach, "Many 'solutions' to this problem have been published on the subject during the last decade, but we yet have to see an effective delivery technology" (see page 956, second paragraph). Nielsen, PE also discuss that a major unmet challenge for the field is to develop methods that allow effective and simple cellular and especially systemic delivery of antisense agents. Nielsen, PE conclude by discussing the eager anticipation of both academic researchers and the pharmaceutical industry for delivery methods for gene therapy drugs.

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods using any GP88 antisense oligonucleotide and any route of GP88 antisense delivery as broadly claimed. The field of nucleic acid-based therapeutics, to date, does not provide guidelines by which oligonucleotide-based therapeutics can be routinely delivered to generally any cell type *in vivo* at a concentration effective to result in inhibition of tumor growth, inhibition of protein expression, or inhibition of tumor proliferation. The specification does not provide specific guidance by which one skilled in the art would expect to be able to systemically deliver a GP88 antisense at a concentration effective to inhibit tumor growth, inhibit GP88 protein expression, or inhibit tumor proliferation *in vivo* as encompassed by the claims.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the

teachings of the instant specification. The quantity of undue experimentation would require the *de novo* determination of those GP88 antisense oligonucleotides that are successfully delivered to target sites in appropriate cells such that tumor growth/proliferation or protein expression are inhibited. The quantity of undue experimentation would also include the determination of how to systemically deliver a GP88 antisense oligonucleotide *in vivo* at a concentration effective to result in the inhibition of tumor growth, the inhibition of protein expression of GP88, or the inhibition of tumor proliferation as claimed. Given the art recognized unpredictability of the therapeutic application of oligonucleotide-based therapeutics a whole organism (*in vivo*), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the breadth of the claims, the state of the art of nucleic acid-based therapy, the level of unpredictability of *in vivo* methods of using oligonucleotide-based therapies, the lack of specific guidance for the *in vivo* application of antisense oligonucleotides for *in vivo* delivery, one skilled in the art would not be able to practice the methods over the full scope claimed without undue trial and error experimentation.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
January 26, 2006